

Outcomes of medical management of peripheral arterial disease in general practice: follow-up results of the PACE-PAD Study

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Title: Outcomes of medical management of peripheral arterial disease in general practice: follow-up results of the PACE-PAD Study

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Abstract: Peripheral arterial disease (PAD), a marker of elevated vascular risk, is highly prevalent in general practice. We aimed to investigate patient characteristics and outcomes of PAD patients treated according to the guidelines versus those who were not.

Methods. PACE-PAD was a multicentre, cluster-randomised prospective, longitudinal cohort study of patients with PAD in primary care, who were followed-up for death or vascular events over 18 months. Guideline-orientation was assumed, if patients received anti-coagulant/antiplatelet therapy, exercise training, and (if applicable) advice for smoking cessation and therapy of diabetes mellitus, hypertension, or hypercholesterolemia, respectively.

Results. The 5099 PAD patients (mean age 68.0 ± 9.0 years, 68.5% males) who were followed-up were in Fontaine stages I, IIa, IIb, III, and IV in 22.5%, 34.6%, 30.1%, 7.8%, and 3.5% (1.5% not specified). Comprehensive guideline orientation was reported in 28.4% only, however, patients in lower Fontaine stages received more often guideline-oriented therapy (I: 30.3%; IIa: 31.6%, IIb: 29.1%, III: 9.8%, IV: 18.0%). During 18 months, 457 patients died (224 due to cerebrovascular or coronary deaths), 319 had instable angina pectoris, 116 myocardial infarction, and 140 an ischemic stroke event. In total, 24% of patients had experienced any vascular event (19.1% a first event). Event rates did not differ between patients treated according to guidelines, and those who were not.

Conclusion. The present PAD cohort was a high-risk sample with an unexpectedly high rate of deaths and vascular events. While physicians appear to focus on the treatment of individual risk factors, rates of comprehensive PAD management in line with guideline recommendations are still suboptimal. Factors contributing to the lacking difference between outcomes in the guideline-oriented and non-guideline-oriented groups may comprise low treatment intensity or other reasons for unsatisfactory effect of treatment, misclassification of events, patient's non-compliance with therapy.

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Response to review comments (7.7.2010)

Dear Professor Kirch,

Thank you for the thorough review of our above manuscript and your interest in reconsidering it for publication in the Journal of Public Health after having received appropriate revisions.

We have carefully addressed the helpful comments of the reviewer point by point as specified on the next page.

We attach the revised text with the changes highlighted in yellow. We hope that the answers are satisfactory to the editors and reviewers and are looking forward to your final decision.

Prof. Dr. David Pittrow

Minor comments:

1. Definitions should be given for compliance and adherence to guide readers.

Response: The current paper deals with guideline orientation (focus on the physician) rather than on compliance and adherence (focus on the patient). Therefore, we omitted the terms compliance and adherence from the key words, and are now using the term "guideline orientation" consistently throughout the paper. Consequently, the definitions are no longer needed.

2. Figure 1: translate "Patienten" into English.

Response: The term has been translated.

3. Figure 2: Use points not commas before decimals. Omit % on top of columns.

Response: This has been addressed.

4. Ref 12: provide volume and page number, not just DOI

Response: This reference has been updated.

In addition, we added 2 additional publications to the reference list, which were published very recently and fit well in the context of this study (Diehm 2010, Meves 2010).

In Tables 4a and 4b the sequence of n and % was changed (now: % (n)), to have a consistent format across all tables.

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Abstract

Peripheral arterial disease (PAD), a marker of elevated vascular risk, is highly prevalent in general practice. We aimed to investigate patient characteristics and outcomes of PAD patients treated according to the guidelines versus those who were not.

Methods. PACE-PAD was a multicentre, cluster-randomised prospective, longitudinal cohort study of patients with PAD in primary care, who were followed-up for death or vascular events over 18 months. Guideline-orientation was assumed, if patients received anticoagulant/antiplatelet therapy, exercise training, and (if applicable) advice for smoking cessation and therapy of diabetes mellitus, hypertension, or hypercholesterolemia, respectively.

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Conclusion. The present PAD cohort was a high-risk sample with an unexpectedly high rate of deaths and vascular events. While physicians appear to focus on the treatment of individual risk factors, rates of comprehensive PAD management in line with guideline recommendations are still suboptimal. Factors contributing to the lacking difference between outcomes in the guideline-oriented and non-guideline-oriented groups may comprise low treatment intensity or other reasons for unsatisfactory effect of treatment, misclassification of events, patient's non-compliance with therapy.

Key words

Guideline orientation, peripheral arterial disease, outcomes, intermittent claudication, observational study.

Background

Substantial advances have been made in the understanding of peripheral arterial disease (PAD) and its implications (Belch et al 2003). A series of studies have shown that PAD is highly prevalent in the primary care setting and the general population. For example, the getABI in 6,880 patients aged at least 65 years found PAD in 21.0% of patients [asymptomatic PAD as evidenced by a low ankle-brachial index [ABI] <0.9 in 12.3%, and symptomatic PAD in 8.7%] (Diehm et al 2009). The German Heinz Nixdorf Recall Study (4814 unselected patients aged 45-75 years) reported PAD in 8.2% in men and 5.5% in women (asymptomatic PAD: 6.4% in men and 5.1% in women) (Kroger et al 2006).

Further, the increasing awareness of the association of PAD with generalised atherosclerosis in other vascular territories has secured its role in primary and secondary prevention of cardiovascular disease. PAD patients carry a high risk of premature death, and of cardiovascular and cerebrovascular events (Meves et al 2010). According to a recent metaanalysis of Heald et al., this risk is doubled, even if all other conventional cardiovascular risk factors are accounted for (Heald et al 2006). This is of particular importance, as PAD signals a risk higher than - for example - smoking or diabetes mellitus, and can therefore guide physicians in selecting patients at particularly high risk. Against the background of the high disease burden of PAD associated with increased risk of vascular events, an aggressive approach to treat cardiovascular risk factors is recommended in all major guidelines, e.g. those of the TransAtlantic Inter-Society Consensus (TASC II) (Norgren et al 2007), the American Heart Association (AHA)/ American College of Cardiology (ACC) (Hirsch et al 2006) and the newly released joint recommendations of the German Society of Angiology (DGA) and other societies.(Deutsche Gesellschaft für Angiologie und Gesellschaft für Gefäßmedizin 2009)

The primary care setting is of particular importance for the management of PAD patients. The family physician needs to be efficient in identifying high risk patients, as he serves as a gatekeeper for the selection of patients for further assessment or treatment by specialists (Grumbach et al 1999), and has a pivotal role in the long-term management of patients (Kröger et al 2010).

While in other countries the situation of PAD patients in primary care has been repeatedly addressed (Hirsch et al 2001, Khan et al 2007), corresponding data from the German healthcare system are limited. Against this background, the Patient Care Evaluation - Peripheral Arterial Disease (PACE-PAD) Study was initiated. We have previously described the baseline results of the study, with focus on the current diagnostics and therapy (i.e., management) of patients with newly diagnosed, suspected or confirmed PAD, with particular focus on the interaction between general physician and specialist care.(Neumann et al 2009) In the present article on the 18-month follow-up, we report (1) the differences of patient characteristics and other factors between patients treated according to guidelines and those who were not and (2) the outcomes of guideline-oriented therapy on the incidence of cardiovascular, cerebrovascular or peripheral vascular events in patients with newly diagnosed PAD.

Methods

Design and study flow

PACE-PAD is a multicentre, cluster-randomised, observational, non-interventional prospective longitudinal study, which followed patients with confirmed PAD in stage Fontaine I-IV at 3 visits over 18 months (Figure 1). The study was conducted according to the principles of “Good Epidemiological Practice (GEP)” (Arbeitsgruppe Epidemiologische Methoden der Deutschen Arbeitsgemeinschaft Epidemiologie (DAE)). Protection of patient and centre data was ensured. According to a statement of the legal department of the University Duisburg-Essen, for this non-interventional study a formal approval was not necessary.

-here insert Figur 1-

Study course

Baseline. Patients were eligible for inclusion, if they had *suspected symptomatic PAD*, i.e., newly diagnosed intermittent claudication (IC) or IC-like complaints with PAD suspected by the treating physician. Further, patients with *suspected asymptomatic PAD* were eligible for inclusion, if they were aged 55 years or above *and* had (1) previous myocardial infarction and/or (2) previous ischemic stroke and/or (3) manifest type 1 or type 2 diabetes mellitus and/or (4) current smoking (for more than 10 years each). If PAD had been diagnosed prior to baseline, patients were not eligible for further evaluations (exclusion criterion).

Follow-up/longitudinal study. If the suspicion of PAD was confirmed at the baseline visit, patients were followed up for 18 months. Three follow-up visits (F/U 1 at 6 month, F/U 2 at 12 month, and F/U 3 at 18 month) were scheduled to collect the following information: incidence of cardiovascular events (stable or unstable angina pectoris, myocardial infarction or coronary revascularisation with or without stenting), cerebrovascular events (stroke or transient ischemic attacks [TIA], prolonged ischemic neurological deficit [PRIND], revascularisation of the carotids) or peripheral revascularisation or amputation, respectively.

The longitudinal study endpoints were myocardial infarction, stroke or minor/major amputation due to PAD. Further, it was assessed whether patients received guideline-

oriented management during follow-up, which was assessed using 6 quality indicators for each patient, using a standardised questionnaire (Table 1). The quality indicators were defined and assessed by an interdisciplinary board (composed of clinical experts in the fields of angiography, cardiology and neurology as well as a methodical specialist regarding evidenced based medicine). They comprised prescription of exercise training in the Fontaine stages I and II, recommendation of smoking cessation, management of arterial hypertension, diabetes mellitus and hypercholesterolemia as well as the use of antiplatelet therapy. Guideline-oriented treatment was assumed for example, if a patient with diabetes mellitus received dietary measures or at least 1 antidiabetic drug.

-here insert Table 1-

Statistics

The original sample size was calculated based on the assumption that the cumulative incidence of vascular events after 18 months was 6.8% in PAD patients with guideline-oriented therapy versus 9.8% in PAD patients not receiving such therapy. A sample of 3,483 symptomatic patients (of whom at least 85% were assumed to have diagnosed PAD) and of 20,485 patients with risk factors (of whom at least 10% were assumed to have diagnosed PAD) was required to obtain a power of 80% at a significance level of 5%. It was planned, to test primarily the hypothesis that the cumulative incidence of cardiac, cerebrovascular and peripheral vascular events during the follow-up period would be lower in PAD patients with guideline-oriented management compared to PAD patients without such management.

Using cross tables, frequency distributions and descriptive statistics, the distributions of variables between the two patient strata were compared. In all analyses, a 2-sided- or the chi-square p-value <0.05 (to evaluate differences between proportions for two or more than two groups) was considered to denote statistical significance. All analyses were performed with SPSS Version 15 for Windows (SPSS Inc, Chicago, Ill, USA).

Results

Characteristics. Patients were included by 2,768 physicians. The flowchart in Figure 1 displays the disposition of patients in the baseline part of the study, and during the 3 follow-up examinations. Of the 6,129 PAD confirmed patients who were originally included at baseline, 22.5% were in Fontaine Stage I, 64.7% in Stage II, 7.8% in Stage III and 3.5% in Stage IV (1.5% not specified). In Follow-up 1, 4,645 PAD patients (75.8%), in Follow-up 2 4,201 patients (68.5%) and in Follow-up 3 3,910 Patients (63.8%) were documented. Overall there were 5,099 patients with at least one documented follow-up visit which could be included in the analyses.

-here insert Figure 2-

Guideline orientation. Only 28.4% of all PAD patients met all applicable (i.e., up to 6) quality indicators for guideline-oriented treatment. Nonetheless, the majority of PAD patients were to a large extent managed in line with guidelines. Figure 2 shows individual quality indicators and the adherence rates over the whole study period of 18 months. With exception of exercise training intervention (41.8%), guideline adherence rates with regard to the various risk factors were high (82.0% to 92.5%). The great majority of the current smokers received the general advice to stop smoking (90.7%). Management of hypertension, diabetes mellitus, hypercholesterolemia and antiplatelet therapy in line with the respective guidelines, was reported in no less than 88% of the PAD patients each (see details in Figure 3).

-here insert Figure 3-

Characterisation. Table 2 provides an overview of demographic and clinical patient characteristics in the total PAD follow-up cohort, and grouped by guideline-orientation status. There were (limited) differences between groups, particularly with regards to mean patient age and diabetes status. Mean patient age was slightly lower in the group treated according to guidelines compared to the group which was not treated in such a way (66.9 vs. 68.5 years). Diabetes was more prevalent in the latter group. In contrast the rate of patients with previous ischemic events (e. g. myocardial infarctions) and atherothrombotic

manifestations (e.g. angina pectoris) were substantially more frequent in the treatment-orientation group.

-here insert table 2-

An analysis by Fontaine status showed that guideline orientation was higher in the early PAD disease stages: while in stage I 37.1% of patients were treated according to guidelines, in stage III only 9.8% and in stage IV 18.0% were managed accordingly (Table 3).

-here insert table 3-

Outcomes after 18 months. During the 18 month follow-up period in the total PAD cohort, 224 cerebrovascular/coronary deaths, 457 all-cause deaths, 140 ischemic strokes, 116 myocardial infarctions, 100 minor and 68 major amputations were reported (Fig. 4a). Figure 4b displays the overall event rates (first event only) at the different follow-up visits. Overall, there were 973 events reported during the 18 month follow-up period, 468 at Follow-up 1, 280 at Follow-up 2 and 225 at Follow-up 3.

-here insert figure 4a-

-here insert figure 4b-

Table 4a provides an overview of all vascular event rates grouped by guideline-orientation status, Table 4b of first event only. There was a statistically significant difference between the two subgroups with more overall, cerebrovascular, and peripheral events in the group not treated according to guidelines. However, a lower number of vascular deaths (coronary, cerebrovascular) and all-cause deaths were reported in this group (Table 4a).

-here insert table 4a-

With the exception of follow-up 3, where in the group not treated according to guidelines more first events occurred, there was no statistically difference concerning the first event (Table 4b).

-here insert table 4b-

Discussion

While the role of PAD as marker of high risk for cardiovascular disease has been fostered, data regarding to actual everyday care of patients with PAD are limited. According to the present study, firstly, guideline-oriented therapy which accounts for all major quality indicators is the exception rather than the rule. Secondly, unexpected results were noted in terms of long-term outcomes with no major differentiation between the subgroups which were differentiated by orientation vs. non-orientation to guidelines.

In the recent years, a number of studies have investigated treatment rates and intensity in PAD patients. More than a decade ago, one of the most authoritative studies about the treatment situation of PAD patients, PARTNERS, reported relatively low treatment rates in 1,865 PAD patients (54% on antiplatelets; 56% on lipid lowering drugs; 88% on antihypertensives, 85% on antidiabetics). The “German epidemiological trial on Ankle Brachial Index, getABI”, is an ongoing non-interventional study in 6,880 unselected individuals aged 65 years or older to assess risk factor profile, treatment and prognosis of PAD patients in primary care. In the patients with PAD alone assessed at the baseline examination in 2001, antiplatelets were prescribed in 53% (versus 65% if coronary or cerebrovascular disease was present), lipid-lowering agents in 40.0%, antihypertensives in 93.3%, and antidiabetics in 74.4% (Pittrow et al 2003). Further, in the pooled analysis of three large French observational studies (ECLAT 1, PRISMA, APRES), patients with PAD alone received antiplatelets in 78.9%, lipid-lowering agents in 40.4%, antihypertensives in 25.8%, and antidiabetics in 17.0% (Bongard et al 2004). The large contemporary REACH registry reported in patients with manifest PAD and the respective concomitant disease or condition, drug treatment rates of 92% for hypertension, 86% for diabetes, 70% for hyperlipidemia, and 82% for antiplatelet use (Bhatt et al 2006). While at first glance these rates appear satisfactory, in that registry only a minority of patients were at target goals for blood pressure, glucose, cholesterol, body weight and non-use of tobacco (Bhatt, Steg 2006).

Notably, in all reported studies, treatment intensity was dependent on comorbidity: if in addition to PAD, coronary heart disease or cerebrovascular disease was *concomitantly* present, treatment rates had consistently improved.

It should be noted that current treatment recommendations for PAD patients are based on various strength of evidence. The recommendation for smoking cessation (counselling, nicotine replacement, bupropion) is based on evidence level I B (consistent evidence, based on a single randomised or on non-randomised studies), for physical exercise on IA (several randomised studies or metaanalyses available). In contrast, the evidence is considered to be weaker for lipid lowering (level II B), and diabetes treatment (II C). While the evidence for the use of antiplatelet drugs is strong (I A), it should be noted that the underlying data are based on symptomatic patients. While antiplatelet therapy has been recommended in diabetic patients and/or PAD patients (American Diabetes Association 2003, American Diabetes Association 2007), the recent results of the POPADAD study in patients with diabetes and concomitant asymptomatic PAD did not provide evidence to support the use of ASS or antioxidants in primary prevention of cardiovascular events and mortality.(Belch et al 2008) Similarly, in the large Japanese JPAD study, primary prevention in diabetic patients with low dose acetylic salicylic therapy did not reduce vascular event rates (Ogawa et al 2008). Very recently, Fowkes et al reported the results of the AAA study: Among participants without clinical cardiovascular disease, identified with a low ABI based on screening a general population, the administration of acetylic salicylic acid compared with placebo did not result in a significant reduction in vascular events (Fowkes et al 2010).

Other reasons beyond the varying strength of evidence may account for the reluctance of physicians to adhere to the PAD guidelines. Basically, many physicians still underestimate the importance of PAD in relation to CHD or CVD (Belch, Topol 2003). Second, the expectation in the management of younger patients that life style change or other non-pharmacological treatment may be sufficient (Pickering 2003), and in elderly the fear of doing harm by applying too-intensive treatment for example with regards to antihypertensive therapy (Berlowitz et al 1998, Chobanian 2001) accounts for undertreatment. Further, the high number of guidelines in various fields, and their length and complexity makes it difficult for the physician to keep abreast with the plethora of

information. Clinical inertia on the side of physicians might be the result. (Phillips et al 2001)

With respect to outcomes at 1.5 years, in our study the total incidence of deaths and vascular events was 23.5%, an unexpectedly high rate, which hints at the inclusion of patients with advanced disease (or multiple risk factors). For comparison, in PAD patients the 1-year incidences of death plus major vascular events were 8.3% in getABI (Lange et al 2005) and 5.4% in REACH (Steg et al 2007).

For our investigation, we chose a real-life, non-interventional study design in order to obtain data on actual practice patterns. This ensured that various types of PAD patients with a broad variety of concomitant diseases or medications could be investigated. However, when interpreting the results of the present study, several limitations have to be taken into account. First, the study was observational and not randomised, which means that unknown biases cannot be ruled out.(Benson et al 2000, Sinatra et al 2005) While physicians were requested to document eligible patients consecutively, there was no additional log-file of all patients in the practice to exclude possible selection processes. Further, no data are available about those patients who could not be followed up. The rate of lost-to-follow-up patients was substantial (about a quarter), and it can be hypothesized that these patients are less well treated than more compliant patients. No information was collected on reasons why guideline-oriented treatment was not pursued (example: contraindication to exercise training in patients with musculoskeletal disease or due to acute cold). The missing difference between outcomes in the guideline-oriented and non-guideline-oriented groups may be due to various factors, which comprise low treatment intensity and therefore unsatisfactory clinical effect, underestimation of the implications of PAD (Hirsch et al 2007) with resulting patient non-compliance or non-adherence with therapy. Further, a lack of effect in certain subgroups, e.g. missing effect of antithrombotic therapy in the asymptomatic patients as noted in the AAA study(Fowkes, Price 2010), or in the high Fontaine stages, might account for the non-differentiation. Finally, methodological issues cannot be fully excluded, such as misclassification of events.

Conclusions

The present PAD cohort was a high-risk sample with an unexpectedly high rate of deaths and vascular events. The proportion of patients treated comprehensively according to the guidelines was relatively low, which calls for an optimisation. There was a lack of differentiation between the guideline-oriented on non-guideline oriented therapy in terms of outcomes, which may be due to patient-related or other factors, and calls for further research.

Competing interests

The study was supported with an unrestricted grant from Sanofi-Aventis, Berlin, Germany. The authors declare that they have no competing interests.

Authors' contributions

AN, JW, FH and RJ participated in study conception and design, acquisition of data, analysis and interpretation of data, funding acquisition, and drafting and critical revision of the paper for important intellectual content. HP, ED, OO, DP and CD advised on the study design and focussed especially on patients' compliance and coping with disease. US did the sample size calculations and GL the statistical calculations. All authors accept responsibility for the scientific content of the paper.

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Figure 1. Flow chart with disposition of patients

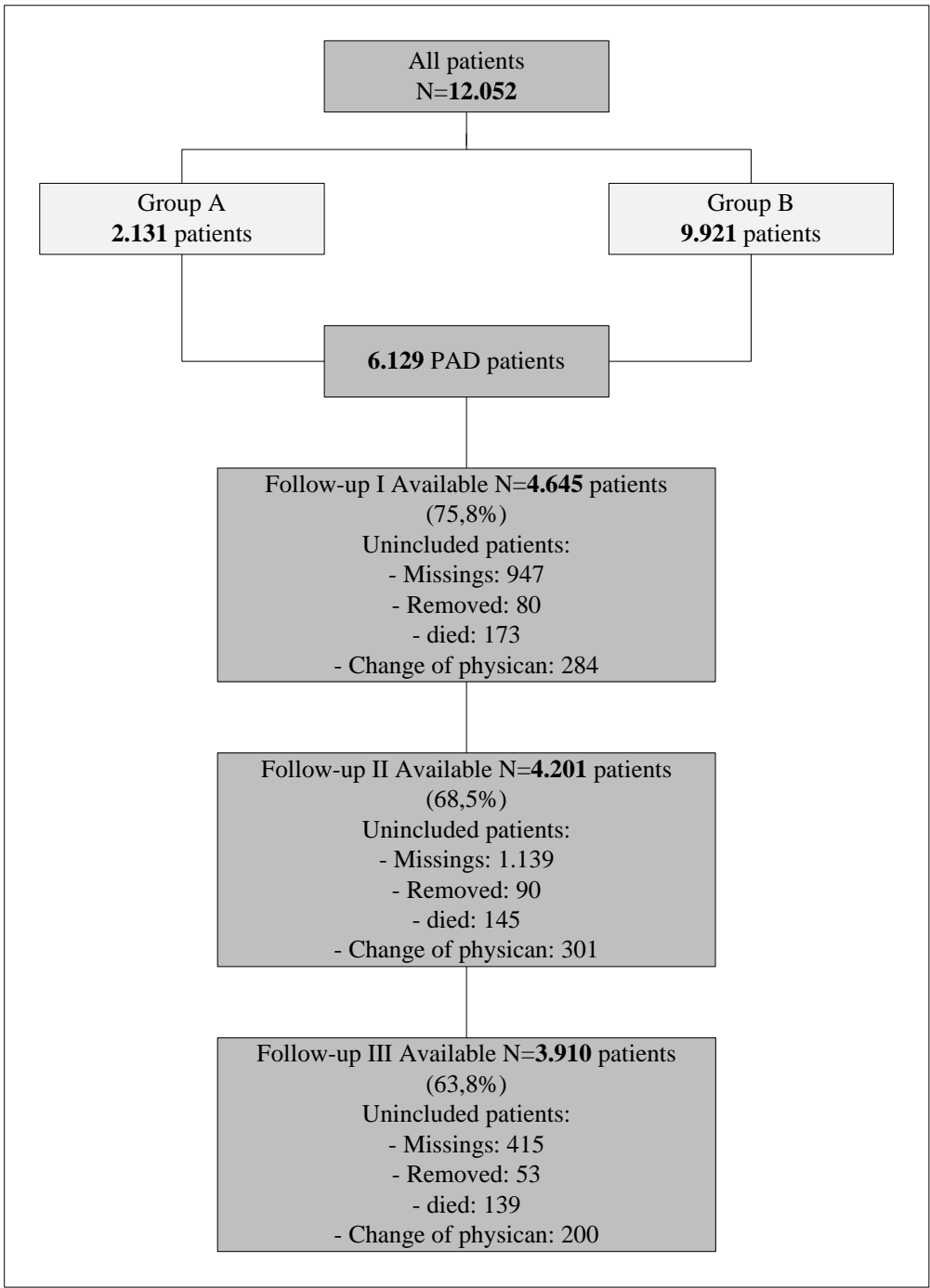


Figure 2. Guideline orientation, by individual quality indicators

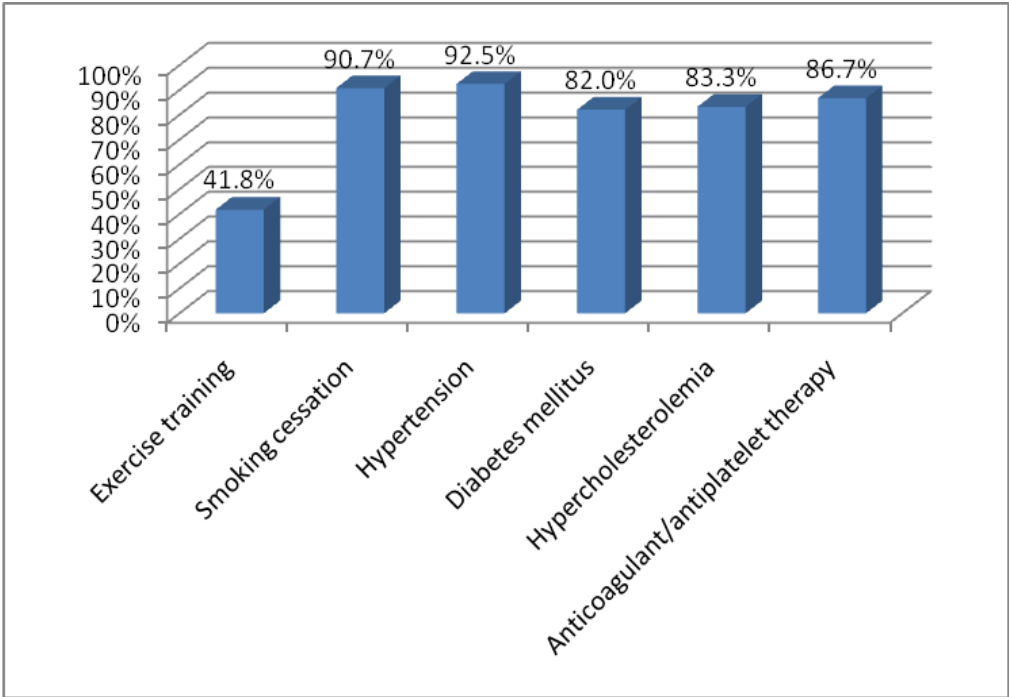
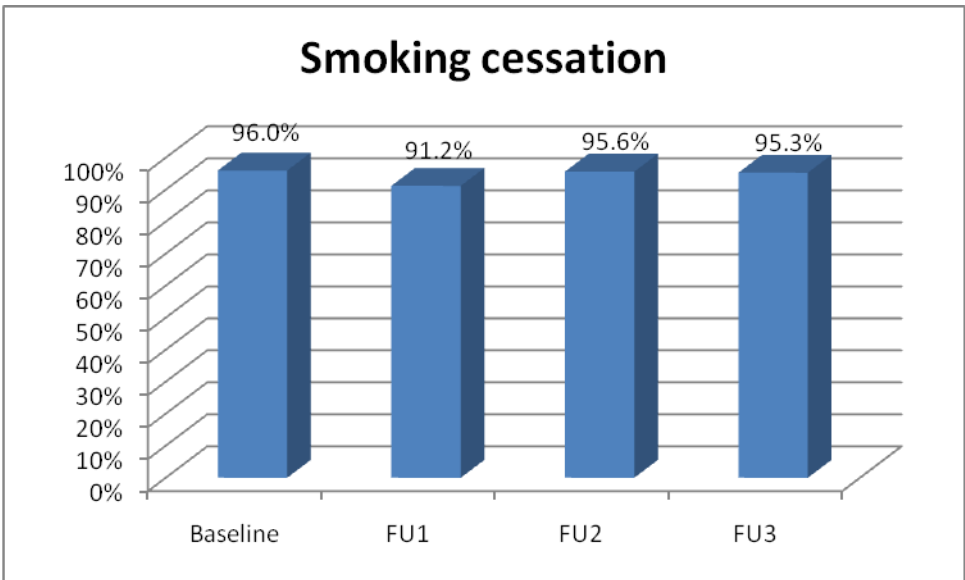
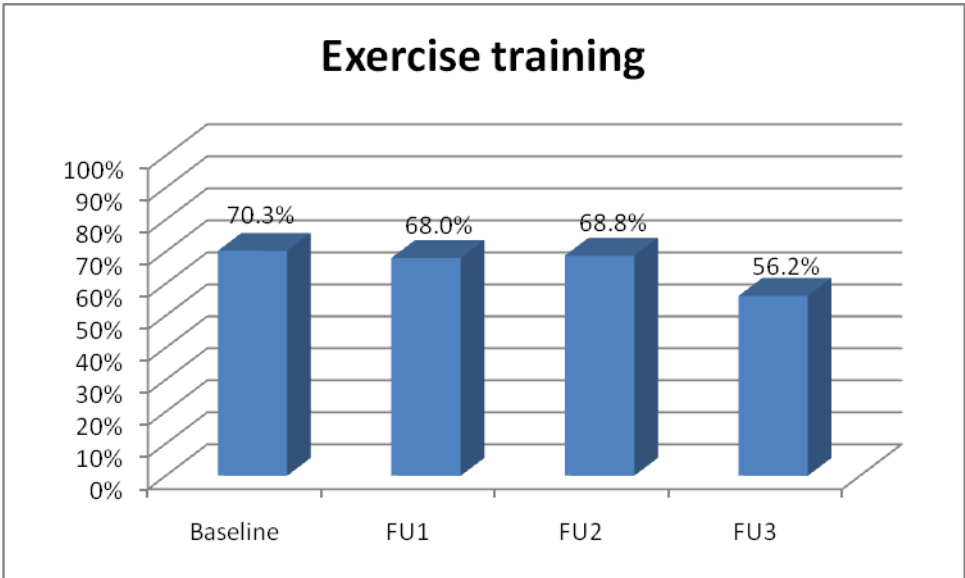
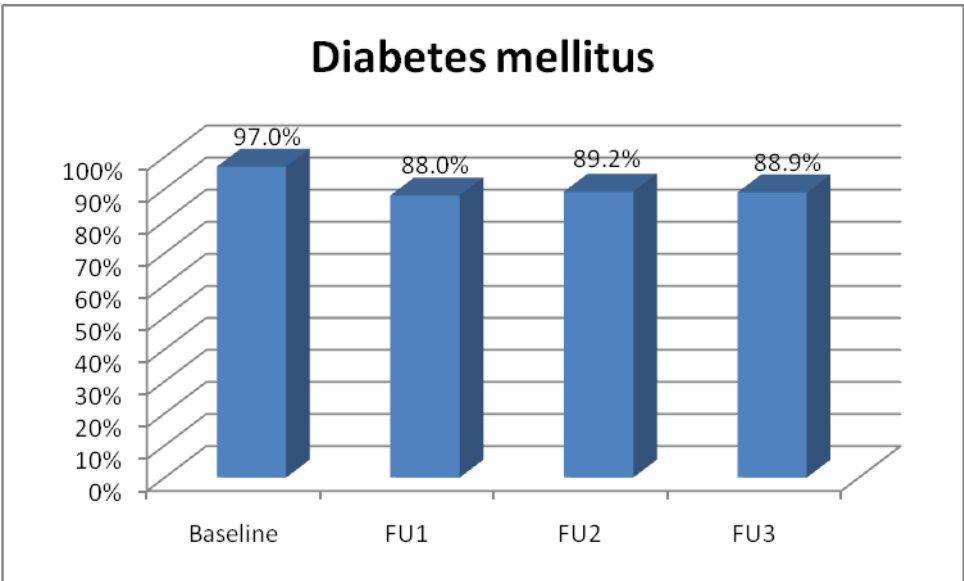
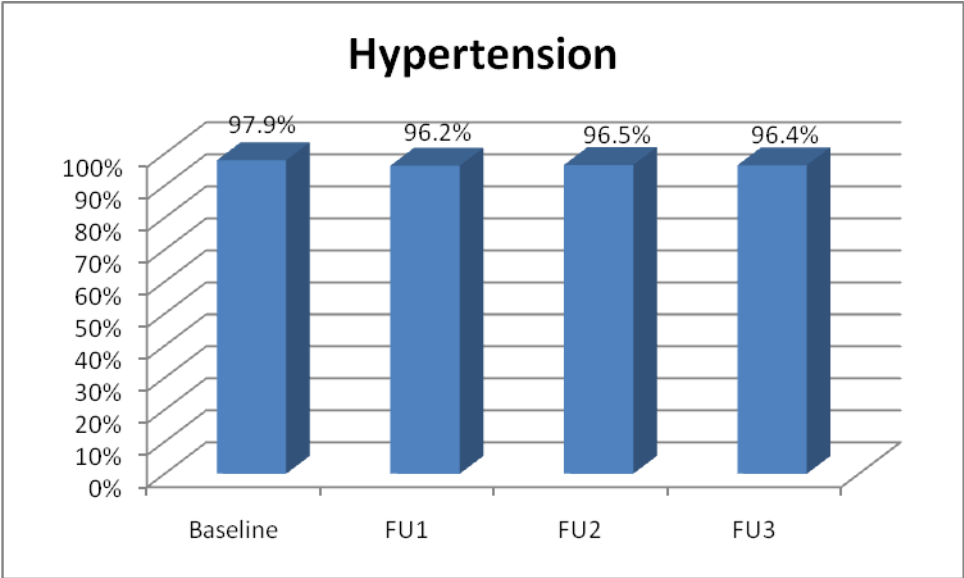


Figure 3. Quantification of guideline orientation, by individual quality indicators over time





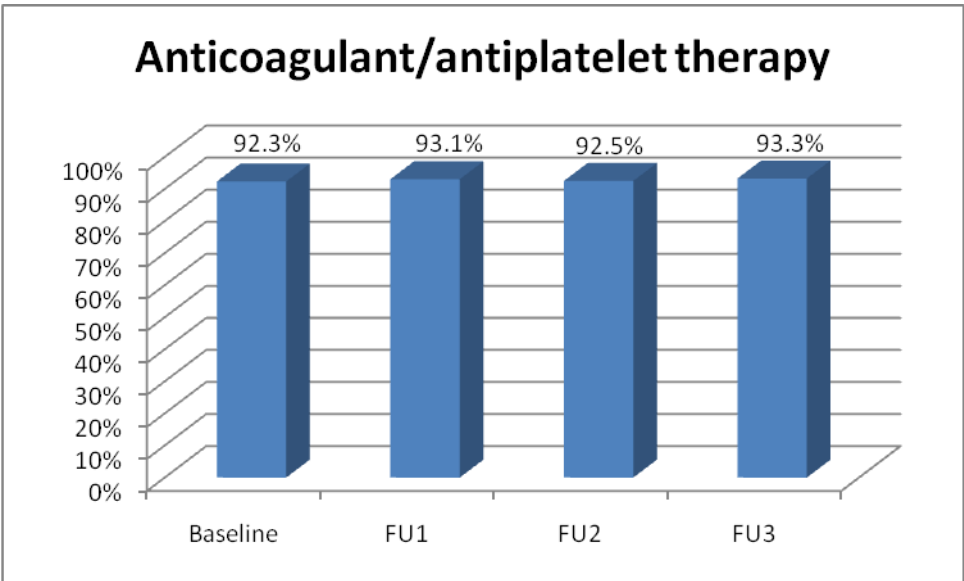
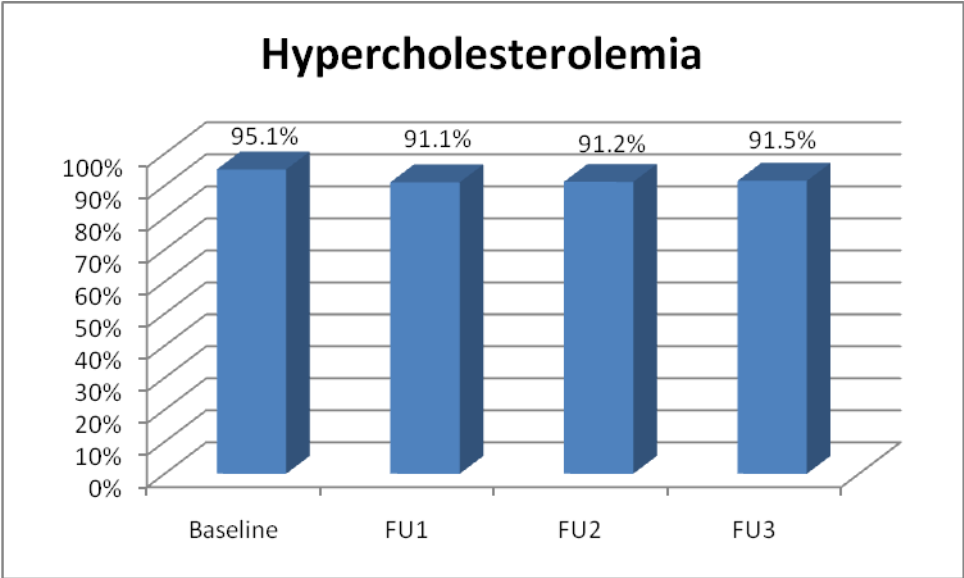


Figure 4a. Outcomes at 18 months (all-cause death and vascular events)

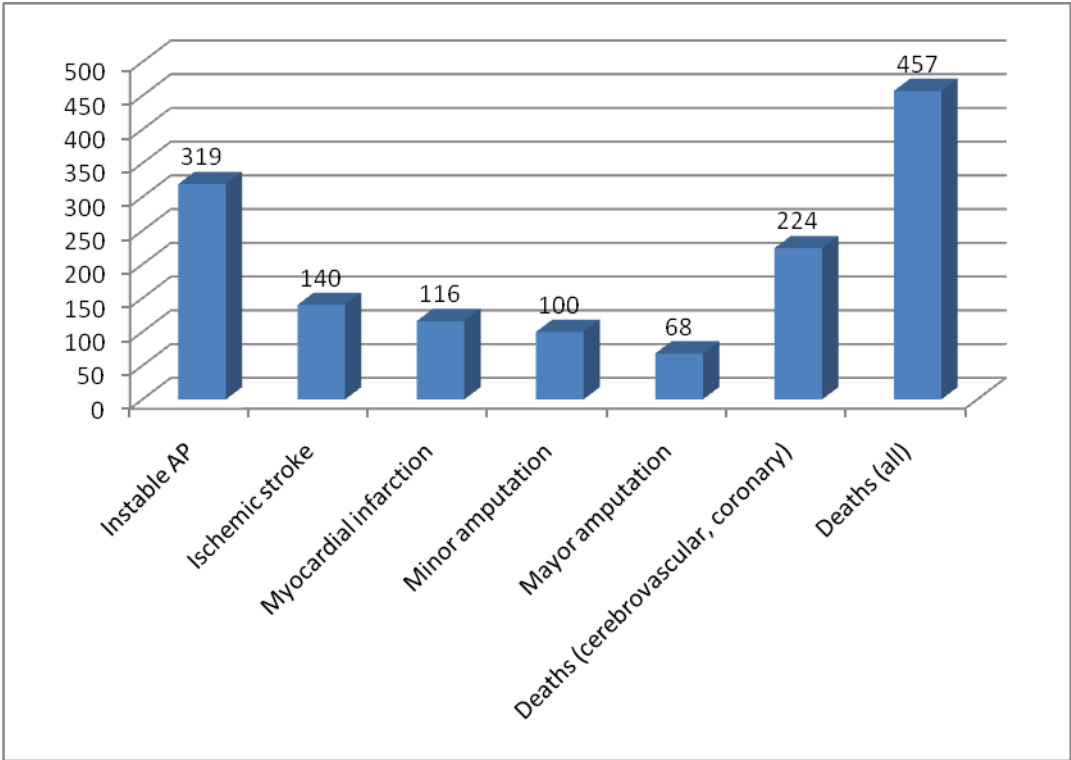


Figure 4b. Outcomes at 18 months (first event)

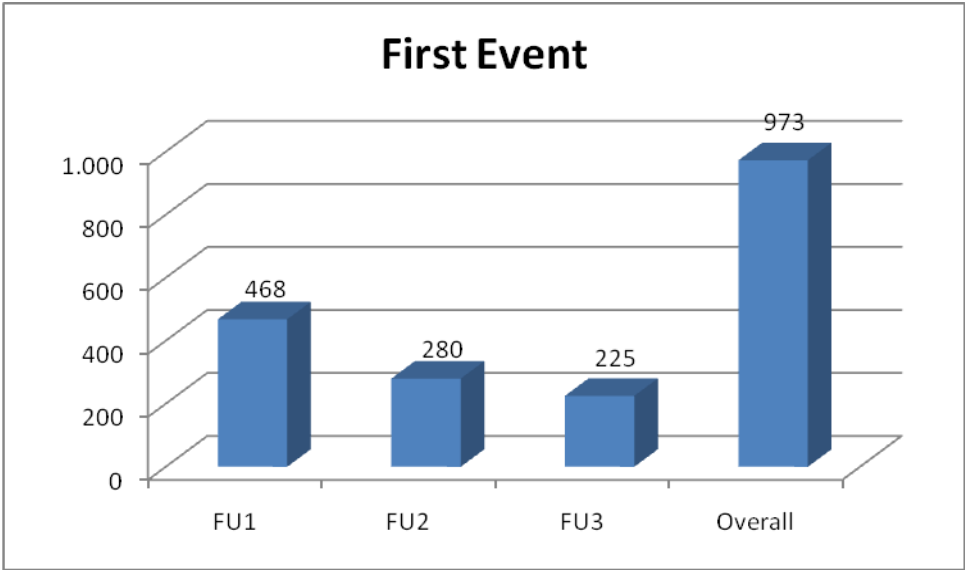


Table 1. Guideline-oriented therapy: definitions of quality indicators

Item	Definition	Specification for Fontaine stage
Anticoagulant/antiplatelet therapy	Prescription of at least 1 drug	II -IV
If present: smoking	Cessation advice, if applicable	All stages
Exercise training	Prescription or recommendation of regular training	I and II only
If present: diabetes mellitus	Dietary measure or at least 1 antidiabetic drug	All stages
If present: hypercholesterolemia	Dietary measure or at least 1 lipid lowering drug	II - IV
If present: hypertension	Dietary measure or at least 1 antihypertensive drug	All stages

Table 2. Fontaine stages in the total cohort, and by overall guideline orientation status

	All PAD patients	PAD treated according to guidelines	PAD not treated according to guidelines	Comparison between PAD subgroups (p value)
	% (N)	% (n)	% (n)	
All patients	100 (5099)	28.4 (1450)	71.6 (3649)	
Fontaine stages				
I (asymptomatic)	100 (1145)	30.3 (347)	69.7 (798)	0.115
IIa (mild claudication)	100 (1765)	31.6 (557)	68.4 (1208)	<0.05
IIb (moderate to severe claudication)	100 (1534)	29.1 (446)	70.9 (1088)	0.521
III (ischemic rest pain)	100 (399)	9.8 (39)	90.2 (360)	<0.05
IV (ulceration or gangrene)	100 (178)	18.0 (32)	82.0 (146)	<0.05
Missing/multiple stages	100 (78)	37.2 (29)	62.8 (49)	<0.05

Table 3. Patient characteristics overall and by guideline-orientation

Parameter	All PAD patients (N=5099)	PAD treated according to guidelines (n=1450)	PAD not treated according to guidelines (n= 3649)	Comparison between subgroups (p value)
Age (years), mean \pm SD	68.0 \pm 9.0	66.9 \pm 8	68.5 \pm 9	<0.05
< 65 years, %	36.2	41.2	34.2	<0,05
\geq 65 years, %	63.8	58.8	65.8	<0,05
Males: females, %	68.5:31.5	72.8:27.2	66.8:33.2	<0.05
Body Mass Index (kg/m ²)	27.7	27.8	27.7	0.33
Systolic and diastolic BP, mean (mmHg)	140.4/82.1	140.0/82.3	140.5/81.9	0.34; 0.15
Complaints (intermittent claudication), %	85.7	85.6	85.7	0.89
Vascular risk factors				
None/1/2/3/4, n	320/2.427/1.815/48 7/50	90/736/560/151/ 15	230/1.691/1.255/336/ 35	0.90
Current Smoking,	53.2 (2711)	52.0 (807)	53.7 (1904)	0.27
> 10 years	94.6 (2565)	93.9 (758)	94.9 (1807)	0.17
Diabetes mellitus	54.9 (2801)	52.0 (807)	56.2 (1994)	<0.05
> 10 years	74.6 (2091)	76.9 (621)	73.7 (1470)	<0.05
Arterial hypertension	76.0 (3877)	77.3 (1199)	75.5 (2678)	0.19
> 10 years	70.3 (2727)	69.8 (837)	70.6 (1890)	0.33
Hypercholesterolemia	69.4 (3537)	70.6 (1096)	68.8 (2441)	0.21

> 10 years	58.9 (2082)	60.4 (662)	58.2 (1.420)	0.11
Carotid stenosis,	11.1 (567)	11.7 (182)	10.9 (385)	0.36
Ischemic events in history (prior to baseline)				
None/1/2/3/4/5/missing	44.4/23.0/21.8/8.2/ 2.3/0.3	40.1/23.1/24.7/9. 2/2.6/0.5	46.3/22.9/20.6/7.7/2. 1/0.4	<0.05
Cerebrovascular: any	23.4 (1.191)	23.9 (371)	23.1 (820)	0.54
TIA/PRIND	15.9 (812)	16.8 (260)	15.6 (552)	0.30
Ischemic Stroke	16.5 (840)	16.2 (252)	16.6 (588)	0.78
Coronary: any	43.0 (2192)	48.1 (746)	40.8 (1446)	<0.05
Stable AP	33.1 (1688)	36.0 (558)	31.9 (1130)	<0.05
Unstable AP	9.6 (488)	11.0 (170)	9.0 (318)	<0.05
Myocardial infarction,	26.8 (1366)	32.4 (503)	24.3 (863)	<0.05

Values indicate % (n), if not specified otherwise. AP, angina pectoris; TIA, transient ischemic attack; PRIND, prolonged reversible ischemic neurological deficit

Table 4a. Vascular events during the 18-month follow-up (F/U 1 to 3, all events)

Parameter	All PAD patients (N=5099)	PAD treated according to guidelines (n=1450)	PAD not treated according to guidelines (n= 3649)	Comparison between subgroups (p value)
	% (n)	% (n)	% (n)	
Coronary	8.6 (435)	8.2 (119)	8.7 (316)	0.25
Cerebrovascular	2.7 (140)	2.1 (30)	3.0 (110)	<0.05
Peripheral	3.3 (168)	1.5 (22)	4.0 (146)	<0.05
Deaths (coronary, cerebrovascular)	4.4 (224)	5.8 (84)	3.8 (140)	<0.05
Deaths (all)	9.0 (457)	12.4 (180)	7.6 (277)	<0.05
Overall	23.5 (1200)	24.2 (351)	23.3 (849)	<0.05

Table 4b. Vascular events during the 18-month follow-up period (first event)

Parameter	All PAD patients (N=5099)	PAD treated according to guidelines	PAD not treated according to guidelines	Comparison between subgroups (p value)
	% (n)	% (n)	% (n)	
FU1	9.2 (468)	10.3 (160)	8.7 (308)	0.07
FU2	5.5 (280)	5.8 (90)	5.4 (190)	0.55
FU3	4.4 (225)	3.4 (52)	4.8 (173)	<0.05
Overall	19.1 (973)	19.5 (302)	18.9 (671)	0.67

Outcomes of medical management of peripheral arterial disease in general practice: follow-up results of the PACE-PAD Study

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